Comments on:

Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling – DRAFT GUIDANCE
Docket Notice: FR Doc. 01-29510

1. Impact of 90% Confidence Criteria – BE Studies

By far the biggest change, relative to that practiced for the last two decades, is imposing the same bioequivalence criteria as has been used for fasting studies (i.e. change from point-estimate criteria to a confidence interval criteria). Invariably this will require larger numbers of subjects to be exposed to test articles. Since food has the potential to make a product with low variability into a product with high variability, much larger studies will potentially be required for fed bioequivalence studies to meet the confidence interval criteria. It is already conceivable that Innovator Companies might seek out processes that endow their product with a unique food-effect signature. No doubt, such changes will be found to be novel in some respect, providing grounds for additional patents. At the same time, Innovators do not appear to be held to the same rigorous a criteria as their ANDA counterparts.

Perhaps the Agency should consider a compromise of existing fasting and fed BE criteria. One possible compromise might be a point-estimate criteria, as follows:

- Fasting or fed bioequivalence studies shall generally be conducted as 2-period crossover studies to complete a minimum of 24 to 36 subjects depending on estimated variability.
- Primary pharmacokinetic parameters shall be calculated as currently done.
- Test and Reference articles shall be deemed bioequivalent when the geometric mean ratio (GMR) is 0.90 to 1.11.
- This criteria will eliminate the burden of powering highly variable drug substances to meet 90% CIs, yet provide reasonable assurance of bioequivalence.

Even for a highly variable drug product, use of at least 30 subjects could provide proof of bioequivalence, provided the point-estimate criteria are met. It could reasonably be argued that meeting the 90% confidence intervals of 80-125% is just a matter of increasing the sample size, especially, if say, a failed 30-subject study has a geometric mean ratio within 0.90-0.111. However, a further consideration should be given to showing that both products have reasonably similar variability. If the CV for the test is less than the reference then there should be no problem. A more variable test product may not be acceptable.

Additionally, fasted and fed studies could be allowed to complete less than 30 subjects, but must complete at least 12 subjects, as long as the 90% confidence interval criteria of 80-125% is met. This would allow products with geometric mean ratios outside 0.9 to 1.11 to pass as is current practice.

2. Standardization of Breakfast Administration

The guidance states that the high-fat breakfast should be consumed over a 30-minute period and immediately followed by administration of the drug product. This specification poses a logistic challenge to the clinic. Firstly, thirty minutes to consume a breakfast is probably a fair bit longer than really required to consume a test meal. To consume a meal over 30 minutes implies that a subject will have to pace his/her-self such that the meal starts and ends in exactly 30 min. Moreover, the meal is expected to finish exactly at 30 min, at which time the test formulation is to be consumed. A perhaps more realistic requirement might be to request that the subject consume the meal over 15 min with dosing 20 min after start of breakfast. Because the meal is in a sense now part of the dosage form itself, standardized administration of the food is as essential as the standardized 240 mL of water required for dosing.

3. Standardization of the Breakfast Contents

The meal description could lend itself to variable interpretation. Since most Sponsors will likely adopt the example given as the test, the description should be better defined. For example, the following might be considered as an example breakfast:

- two grade-A eggs scrambled in 2 tsp butter
- two 2-oz sausage patties, made with 80% lean meat, fried and drained of grease
- two slices of regular-size toast served with 2 tsp butter
- one 4-oz serving of hash browns, drained of grease
- one 8-oz serving of whole milk.

[The caloric breakdown of above meal should be determined.]

Finally it would appear, using a simple "within 10%" statement will decrease the confusion health care providers have in explaining generic products are approved by the FDA if they exhibit a 90% confidence the geometric mean ratio of the generic product is within 80 to 125% of the brand product. The next time you have a conversation with someone about bioequivalence see if you can really get across the concept in less than 30 minutes, if at all. Or even make it simpler: Explain why the limits are 80 to 125 and not 80 to 120.

Arthur B. Straughn, Pharm.D.
Professor and Director UT Drug Research Laboratory
Department of Pharmaceutical Sciences
College of Pharmacy
University of Tennessee, Memphis

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